Drug Class Review

Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder

Final Report
Executive Summary
Update 3

September 2009

Update 2: November 2007
Update 1: May 2006
Original Report: September 2005

The literature on this topic is scanned periodically.

This report reviews information about the comparative effectiveness and safety of drugs within a pharmaceutical class. The report is neither a usage guideline nor an endorsement or recommendation of any drug, use, or approach. Oregon Health & Science University does not endorse any guideline or recommendation developed by users of this report.

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INTRODUCTION

According to the most recent National Institutes of Health Consensus Statement (1998), "attention deficit hyperactivity disorder is the most commonly diagnosed childhood behavioral disorder." Classification of hyperactivity and defects in attention emerged in the 1960's as Minimal Brain Dysfunction and Hyperkinetic Syndrome, and has continued to evolve over time.

A number of community-based studies have reported attention deficit hyperactivity disorder (ADHD) prevalence rates that range from 1.7% to 16%. This is broader than the range of 3% to 5% that was estimated by the expert panelists that participated in the National Institutes of Health Consensus Development Conference on Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder in 1998. The estimated prevalence cited in the most recent (1997) version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) is 3% to 7%. Differences in prevalence estimates may be due to variation in methods of ascertainment and diagnostic criteria. While no independent diagnostic test exists for ADHD, the DSM-IV provides standardized criteria that can be used as a foundation for clinical diagnosis. According to the DSM-IV, essential features of ADHD include persistent levels of inattention, impulsivity, and/or hyperactivity that exceed usual developmental patterns. In order to qualify for a DSM-IV diagnosis of ADHD, symptoms must date back to before age 7, persist for at least 6 months, and cause impairment that interferes with functional capacity in at least 2 performance settings (social, academic, or employment). DSM-IV specifies 3 distinct subtypes of ADHD that are characterized by predominantly inattentive, hyperactive-impulsive, or mixed symptoms.

Scope and Key Questions

The purpose of this review is to compare the benefits and harms of different pharmacologic treatments for ADHD. Included drugs are described in Table 1.

Table 1. ADHD drugs and indication (immediate-release and extended-release formulations)

Active ingredient(s)	Referred to in this summary as	Trade name[a]	Forms
Amphetamine mixture (amphetamine aspartate; amphetamine sulfate; dextroamphetamine saccharate; dextroamphetamine sulfate)	MAS IR	Adderall®[a,b]	Oral tablet
	MAS XR	Adderall XR®	Extended-release oral capsule
Atomoxetine HCl	Atomoxetine	Strattera®	Oral capsule
Dexmethylphenidate hydrochloride	d-MPH IR	Focalin®[a,b]	Oral tablet
	d-MPH ER	Focalin XR®[b]	Extended-release oral capsule
Dextroamphetamine sulfate	DEX IR	Dexedrine®[a]	Oral tablet
		Dextrostat®[a,d]	Oral tablet
		Liquadd®	Oral solution
	DEX SR	Dexedrine Spansule®	Sustained-release oral capsule
Lisdexamfetamine dimesylate	Lisdexamfetamine	Vyvanse™[d]	Oral capsule
Methamphetamine hydrochloride	Methamphetamine	Desoxyn®[b]	Oral tablet

Active ingredient(s)	Referred to in this summary as	Trade name[a]	Forms
Methylphenidate hydrochloride	MPH OROS	Concerta®	Extended-release oral tablet
	MPH transdermal	Daytrana®[b]	Transdermal patch
	MPH CD	Metadate CD®[b]	Extended-release oral capsule
	MPH ER	Metadate ER®[b]	Extended-release oral tablet
		Medikinet®[c]	Extended-release oral tablet
	MPH chewable MPH solution	Methylin®[b]	Oral chewable tablet Oral solution
	MPH IR	Ritalin®[a]	Oral tablet
	MPH LA	Ritalin LA®[b]	Extended-release oral capsule
	Multi-layer MPH	Biphentin®[c]	Extended-release oral capsule
	MPH SR	Ritalin SR®	Extended-release oral tablet
Modafinil	Modafinil	Provigil®	Oral tablet
		Alertec®[c]	Oral tablet

[a] Or generic equivalent.
[b] Not available in Canada.
[c] Not available in the United States.
[d] Approved in Canada but not commercially available.

The participating organizations of the Drug Effectiveness Review Project approved the following key questions to guide this review:

1. Evidence on Effectiveness and Efficacy
    a. What is the comparative or noncomparative evidence that pharmacologic treatments for attention deficit disorders improve *effectiveness* outcomes?
    b. What is the *comparative* efficacy of different pharmacologic treatments for attention deficit disorders?

2. Tolerability, Serious Adverse Events, Misuse and Diversion
    a. What is the evidence of *comparative* tolerability of different pharmacologic treatments for attention deficit disorders?
    b. What is the evidence of serious adverse events or long-term adverse events associated with use of pharmacologic treatments for attention deficit disorders?
    c. What is the comparative or noncomparative evidence that pharmacologic treatments for attention deficit disorders impact the risk of misuse or illicit diversion in patients with no history of misuse or diversion?
        i. Stimulants compared with nonstimulants
        ii. Immediate release compared with intermediate compared with long-acting formulations
        iii. Any included pharmacologic treatment

3. Evidence in Subgroups of Patients
    a. What is the evidence of benefits and harms of pharmacologic treatments for attention deficit disorders in subgroups of patients based on demographics (age, racial groups, gender), other medications or therapy, or comorbidities (e.g. tics, anxiety, substance use disorders, disruptive behavior disorders)?
    b. What is the comparative or noncomparative evidence of misuse or illicit diversion of pharmacologic treatments for attention deficit disorders in patients with current or past substance use disorder comorbidities?
        i. Stimulants compared with nonstimulants
        ii. Immediate release compared with intermediate compared with long-acting formulations
        iii. Any included pharmacologic treatment

METHODS

Literature Search

To identify relevant citations, we searched the Cochrane Central Register of Controlled Trials (1st Quarter 2009), Cochrane Database of Systematic Reviews (1st Quarter 2009), MEDLINE (1996 to April Week 4 2009), and PsycINFO (1806 to April Week 4 2009) using terms for included drugs, indications, and study designs. We have attempted to identify additional studies through searches of reference lists of included studies and reviews, the US Food and Drug Administration web site, as well as searching dossiers submitted by pharmaceutical companies for the current review.

Validity Assessment

We assessed the internal validity (quality) of trials based on the United States Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (U.K.) criteria. We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. Trials that had a fatal flaw in one or more category were rated “poor-quality”; trials that met all criteria were rated “good-quality”; the remainder were rated “fair-quality.” A fatal flaw occurs when there is evidence of bias or confounding in the trial, for example when randomization and concealment of allocation of random order are not reported and baseline characteristics differ significantly between the groups. In this case, randomization has apparently failed and for one reason or another bias has been introduced.

RESULTS

Overview

Overall, we included 369 studies, 71 of these were added in Update 3. Of these, 69 were direct comparisons of one drug versus another in a randomized, controlled trial. Dossiers were submitted by Eli Lilly (atomoxetine HCl), Shire US (lisdexamfetamine dimesylate and transdermal methylphenidate), and McNeil (methylphenidate OROS) for the most recent update of this report.

There were no *trials* of comparative effectiveness of these drugs for treatment of ADHD and good-quality evidence on the use of drugs to affect outcomes relating to global academic performance, consequences of risky behaviors, social achievements, etc. was lacking. The evidence for comparative efficacy and adverse events of drugs for treating ADHD was severely limited by small sample sizes, very short durations, and the lack of studies measuring functional or long-term outcomes. Methods of measuring symptom control vary significantly across studies. The crossover design was frequently used, with few analyzing the effect of order of administration of drugs. Those that did found a significant effect. No head-to-head efficacy trial was good quality. The small numbers of patients in these trials limited the ability to show a difference between drugs if one exists.

Limitations to the generalizability of these trials included limited characterization of ADHD symptomatology across studies due to use of varied or indeterminate diagnostic processes and underrepresentation of minorities and the most seriously ill patients. The small sample sizes of these trials did not allow for statistical analyses of potential effects of these factors.

Overall, the rate of response to stimulants appeared to be in the range of 60% to 80%, however the definitions of response rate varied and may not be comparable. Depending on the definition used, there is lack of clarity on the relationship of response rate to clinical significance. Response rates of nonstimulants varied, but the range in placebo-controlled trials was similar to that found with stimulants. Significant variation in the method of assessment and definition of response was most likely the reason for the wide variation.

SUMMARY

Results by key question are summarized in Table 2, below.

Table 2. Summary of the evidence

	Comparison: Overall strength of the evidence	Conclusion
Key Question 1. Benefits		
General		
Effectiveness	No trials found: Poor	No conclusions about comparative effectiveness of different drugs for ADHD can be made.
Young children		
Efficacy	Overall: Poor	
	MPH IR	The evidence on efficacy of MPH IR in the short term is mixed.
Children		

	Comparison: Overall strength of the evidence	Conclusion
Efficacy	Overall: Fair (individual ratings below)	
Stimulants		
IR vs. SR formulations	MPH IR vs. MPH SR: Fair	Studies of MPH IR vs. extended release formulations in children generally were unable to identify significant differences in symptom improvement. Studies of MPH IR and MPH OROS are conflicting; a difference was not found in double-blind studies while open-label studies indicate greater improvement with MPH OROS on some measures.
SR vs. SR formulations	MPH SR vs. MPH SR formulations: Poor	Limited evidence from 2 small crossover studies suggests that MPH LA was superior to MPH OROS on some, but not all efficacy outcomes. Limited evidence suggests that MPH CD was superior to MPH OROS on outcomes in the morning; they had similar effects in the afternoon; and MPH OROS was superior in the evening. d-MPH ER was superior to MPH OROS at 2 to 6 hours post-dose, and MPH OROS was superior at 10 to 12 hours in 1 trial.
IR vs. IR	DEX IR vs. MPH IR: Good	The body of evidence clearly indicates no difference in efficacy between DEX and MPH IR.
	MAS IR vs. MPH IR: Fair	MAS IR was superior to MPH IR on a few efficacy outcome measures in 2 trials, but clear evidence of superiority is lacking.
	DEX IR vs. DEX ER vs. MAS: Poor	Evidence on the comparison of DEX IR vs. SR vs. MAS may suggest that measures made in the morning show DEX IR superior to DEX SR, and afternoon measures show DEX SR superior to MAS.
	Modafinil vs. MPH IR: Fair	Based on 1 trial, modafinil was similar to MPH IR in efficacy
	Dexmethylphenidate: NA	Only placebo-controlled evidence was found.
Transdermal MPH	Transdermal MPH vs. MPH OROS	Based on 1 trial, MTS and MPH OROS had similar efficacy
Lisdexamfetamine	Fair	Lisdexamfetamine was comparable to MAS XR on average SKAMP-DS scores and superior to placebo on same, as well as on ADHD rating scale IV mean changes.
Atomoxetine	Poor	
	Atomoxetine vs. MPH IR	Limited evidence suggests a lack of a difference in efficacy compared to MPH IR.
	Atomoxetine vs. MAS XR	Limited evidence suggests that MAS XR is superior to atomoxetine on most efficacy measures.
	Atomoxetine vs. MPH OROS	MPH OROS was superior to atomoxetine in response rates
Adolescents		
Efficacy	Poor	
	MPH OROS vs. MAS IR	Effectiveness outcomes: NR Short-term improvements in core ADHD symptoms: No differences. Other: MPH OROS > MAS IR on overall simulator driving performance.
	MPH IR vs. MPH OROS	Functional capacity: NR Short-term improvements of core ADHD symptoms: NR. Driving performance: MPH OROS > MPH IR in evening and at night.
	Placebo-controlled studies of MPH IR	Functional capacity: NR Short-term improvements of core ADHD symptoms: MPH IR generally efficacious.
Adults		
Efficacy	Fair	
Direct comparisons	DEX IR vs. modafinil	Limited evidence suggests a lack of a difference in efficacy between DEX IR and modafinil.

	Comparison: Overall strength of the evidence	Conclusion
Indirect comparisons	Atomoxetine, DEX IR, d-MPH XR, lisdexamfetamine, MPH ER, MPH IR, MPH SR, MPH OROS, MAS IR, MAS XR: Fair	All were found to be effective short-term treatments for reducing ADHD symptoms in placebo-controlled trials. Pooled analyses suggest a relative benefit of clinical response for shorter acting stimulants at 3.26 times greater than for patients taking longer-acting stimulants (95% CI, 2.03 to 5.22). Atomoxetine: Not consistently significantly superior to placebo in improving quality of life and driving performance outcomes MPH IR: Consistently superior to placebo in improving driving performance outcomes. MAS XR: Superior to placebo in improving overall simulated driving performance in 1 trial
	d-MPH IR, MPH transdermal patch, Metadate CD, Ritalin LA®, and Biphentin®; Poor	No evidence.
Key Question 2. Safety		
2b. Short-term trial evidence		
Young children	1 placebo-controlled trial of MPH: Poor	Indirect comparisons cannot be made; MPH associated with higher rates of adverse events than placebo.
Children	Poor	Very few studies reported methods for assessing adverse events a priori.
	MPH IR vs. MPH SR	There is no evidence of a difference in adverse events between IR and SR formulations.
	MPH SR vs. MPH SR formulations	No differences in adverse events were found.
	DEX vs. MPH IR	Limited evidence from short-term trials suggests that weight loss is greater with DEX than MPH IR.
	MAS vs. MPH IR	Very limited evidence suggests that twice daily dosing of MAS led to higher rates of loss of appetite and sleep trouble.
	DEX IR vs. DEX ER vs. MAS	Transient weight loss was greater with MAS and DEX SR than with DEX IR.
	Comparisons to atomoxetine	Rates of vomiting ranged from 12% to 13% for atomoxetine, which was approximately 3 times greater than rates for MPH IR or MAS XR. Rates of somnolence ranged from 6% to 26% for atomoxetine, which was 3 to 4 times greater than rates for longer-acting stimulants (MPH OROS and MPH XR) and over 7 times greater than rates in trials of MPH IR. Nausea and anorexia were greater with atomoxetine compared to MPH IR in 1 trial. MPH OROS and MAS XR caused higher rates of insomnia (7% atomoxetine, 13% MPH OROS, 28% MAS XR) than atomoxetine in 2 trials.
	Lisdexamfetamine	No differences in adverse event rates between lisdexamfetamine vs. MAS XR.
Teens	Poor	Very few studies reported methods for assessing adverse events a priori.
	Placebo-controlled studies of MPH IR	No indirect comparisons possible. Placebo-controlled trials only involved assessment of MPH IR.
Adults	Poor	Very few studies reported methods for assessing adverse events a priori. Rates of appetite disturbance and sleep disturbance were generally greater for atomoxetine, DEX IR, d-MPH-ER, lisdexamfetamine, MPH ER, MPH IR, MPH SR, MPH OROS, MAS IR, and MAS XR Our adjusted indirect meta-analysis found that shorter-acting stimulants, longer-acting stimulants, and atomoxetine groups had significantly higher risk of appetite loss and sleep disturbance relative to placebo, but indirect comparisons suggest no significant difference between drug types.

	Comparison: Overall strength of the evidence	Conclusion
	Adderall and MPH IR	Indirect comparisons from placebo-controlled trials suggest both are associated with higher rates of insomnia, appetite loss and withdrawal due to adverse events than placebo.
	DEX IR and MPH SR	Indirect comparisons cannot be made.
	Atomoxetine	Very limited indirect comparative evidence across few placebo-controlled trials suggests that atomoxetine is associated with rates of insomnia, appetite loss and withdrawals due to adverse events similar to stimulants.
2b. Long-term safety: Observational studies		
Mixed populations, primarily children	Fair	
	Sudden cardiac death	Increased risk associated with current stimulant use (odds ratio 7.4; 95% CI, 1.4 to 74.9) based on case control study. Smaller study found no association. Recall bias may be an issue.
	Cardiac events	Emergency room and physician office visits for cardiac causes significantly more frequent among those taking stimulants compared with those not (hazard ratio, 1.20; 95% CI, 1.04 to 1.38 compared with hazard ratio, 1.21; 95% CI, 1.06 to 1.30).
	Suicidal behavior	Increased risk with atomoxetine compared to placebo (risk difference, 0.52; 95% CI, 0.12 to 0.91) based on meta-analysis. Time to onset of behavior 9 to 32 days. Overall rate of suicidal behavior and ideation was 0.44% in this study compared to 1.7% in another meta-analysis of longer-term duration.
	Height	• DEX vs. MPH IR: Mixed findings. DEX=MPH in 6-year height increases in 1 study; DEX>MPH in 2-year height decreases in the other. • MPH IR vs. unmedicated controls: No significant differences in 2 studies. • MPH IR in uncontrolled studies: Inconsistent effects across 4 studies. • Atomoxetine: Uncontrolled studies suggest that height changes are similar to those reported with MPH IR, and are also transient.
	Weight	• DEX vs. MPH: Three studies consistently suggest that DEX>MPH in weight gain suppression in the first 1-2 years. The longest-term (5 years) of these studies also reported that DEX=MPH in exceeding weight gain expectations at final follow-up. These findings are weakened by methodological flaws, however. • MPH IR in other comparative (imipramine and unmedicated hyperactives or healthy controls) and noncomparative studies: Evidence does not support an indisputable relationship between MPH and weight gain suppression. • MPH OROS and tomoxetine (atomoxetine): Evidence from noncomparative studies (1 each) doesn't suggest weight gain suppression effects. • Atomoxetine: Uncontrolled studies suggest that weight changes are similar to those reported with MPH IR, and are also transient.
	Tics, seizures, cardiovascular adverse events, injuries, and suicidal behavior	No comparative evidence.
2c. Abuse/diversion		
Teens and young adults	Poor	Stimulant use during childhood not associated with alcohol abuse later. May be protective against or delay nicotine dependence, but comorbid conduct disorder may be a significant confounder. Stimulant use may protect against later substance abuse, but again comorbid conduct disorder may be a confounder. Evidence on misuse and diversion reports wide ranges of prevalence with no comparative data.

	Comparison: Overall strength of the evidence	Conclusion
Key Question 3. Subgroups		
Children	Fair	
	ADHD subtypes or severity	Atomoxetine, MPH IR, MPH OROS all have superior efficacy relative to placebo in children with ADHD, regardless of diagnostic subtype but response may be better in those with combined or inattentive subtype.
	Race/ethnicity	Most trials conducted in primarily White populations. Ethnicity/race only reported in one half of studies. No analyses based on race. Very limited evidence suggests MPH IR in African American boys results in response rates similar to other populations studied. Evidence from subgroup analysis of a placebo-controlled trial suggested that effects of lisdexamfetamine may be less robust in non-Caucasian children.
	Gender	Subgroup analyses based on gender were limited. Evidence from subgroup analysis of a placebo-controlled trial suggested that lisdexamfetamine may be less efficacious in girls. Exploratory analysis indicates atomoxetine may have better response on emotional regulation items in women than men.
	Tic disorders	No consistent evidence that atomoxetine, DEX IR or MPH IR increased tic severity or frequency compared to placebo. All of these studies of MPH IR showed a benefit of MPH IR on ADHD outcome measures compared to placebo.
	Oppositional defiant disorder	Very limited evidence suggests that atomoxetine is beneficial on most ADHD outcomes compared to placebo.
	Bipolar disorder	Very limited evidence suggests that MAS IR or MPH IR have benefit on most ADHD outcomes compared to placebo.

Abbreviations: ADHD, attention deficit hyperactivity disorder.